Endometrial Cancer
The Old Merges with the New
Lora Hedrick Ellenson, M.D.

Objectives

Intermediate Level - Endometrial cancer consists of several morphologically and biologically distinct tumors. This lecture will provide an overview of new advances in our understanding of endometrial carcinoma. The lecture will present information ranging from the clinical presentation to gross and microscopic analysis as well as newer molecular studies.

Goals - The learner will understand:
Endometrial cancer is more than one disease
The major types of endometrial cancer
The clinical relevance in the distinction of different types of endometrial cancer

Objectives - The learner will be able to:
Adequately gross hysterectomy specimens for the different types of endometrial cancer
Know the important gross and clinical findings important in an endometrial cancer diagnosis
Determine the important details of the history and gross findings relevant to rendering the correct diagnosis of endometrial cancer

UTERINE CORPUS: TWO COMPONENTS

Endometrium
Epithelial (glandular)
Stromal

Myometrium
Smooth muscle
Normal Menstrual Cycle

- **Proliferative**
  - Estrogen driven
  - Proliferation of epithelium is regulated by GF produced by the stroma

- **Secretory**
  - Progesterone driven
  - Proliferation is terminated and both components differentiate

Endometrial Glandular Configurations

- **A. Early proliferative glands**
- **B. Mid proliferative glands**
- **C. Late proliferative glands**
What is Cancer?

- Normal Cells
- Genetics
- Environment
- Multiple Alterations
- Defective Cell Eliminated

Uncontrolled growth of cells in the body.
Cells circumvent tight controls set in place in tissues.
Mutations in tumor suppressor and oncogenes cause cells to overcome all inhibitory signals.

Abnormal Cell Growth: Oncogenes

- Normal genes (regulate cell growth)
- 1st mutation (leads to accelerated cell division)
- Mutated Protein

Tumor Suppressor Genes

- Normal genes (regulate cell growth)
- 1st mutation (susceptible carrier)
- 2nd mutation or loss (leads to cancer)
- No brakes!
- Active oncogene
Endometrial Carcinoma

Endometrial carcinoma is the most common invasive tumor of the female genital tract.

In the US, it is the fourth most common cancer in women and worldwide, it is the fifth most common cancer.

Incidence varies widely in the world.

In the US, incidence is twice as common in whites compared to blacks, but death is higher in blacks due to increase in high-risk cancers.

Most cases are sporadic but cases are hereditary forms exist.

Classification of Endometrial Carcinoma

<table>
<thead>
<tr>
<th>Pathogenetic forms of endometrial carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Normal epithelium</td>
</tr>
<tr>
<td>Menopausal status</td>
</tr>
<tr>
<td>Preovulatory phase</td>
</tr>
<tr>
<td>Tumor grade</td>
</tr>
<tr>
<td>Menopausal onset</td>
</tr>
<tr>
<td>Histologic subtypes</td>
</tr>
<tr>
<td>Behavior</td>
</tr>
<tr>
<td>Genetic alterations</td>
</tr>
<tr>
<td>p53 mutation</td>
</tr>
</tbody>
</table>

Endometrial Tumorigenesis

- Estrogen
- SH → CH → CAH → Endometrioid Ca (Type I)
- Atrophy
- EIC → Serous Ca (Type II)
ENDOMETRIAL HYPERPLASIA

- Abnormal proliferation of glands
- Exogenous/endogenous estrogen stimulation or idiopathic
- Classification is based on cytology and architecture
- Constitutes a morphological continuum to carcinoma

Endometrial Hyperplasia

<table>
<thead>
<tr>
<th>Classification of endometrial hyperplasia</th>
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<tbody>
<tr>
<td>Hyperplasia without atypia</td>
</tr>
<tr>
<td>Simple hyperplasia without atypia</td>
</tr>
<tr>
<td>Complex hyperplasia without atypia</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>Simple atypical hyperplasia (very rare)</td>
</tr>
<tr>
<td>Complex atypical hyperplasia</td>
</tr>
</tbody>
</table>
HYPERPLASIA WITHOUT ATYPIA

• Simple Hyperplasia
  - Minimal glandular complexity
  - Stroma remains abundant
  - No cytological atypia
  - 1% progress to carcinoma

• Complex Hyperplasia
  - Increased glandular complexity with decreased stroma; glands can be nearly back-to-back
  - No cytological atypia
  - 3% progress to carcinoma
HYPERPLASIA WITH ATYPIA

- Simple Hyperplasia
  - Very rare

- Complex Hyperplasia
  - Increased glandular complexity with decreased stroma; glands can be nearly back-to-back
  - Cytological atypia
  - 25-40% progress to carcinoma

Complex Atypical Hyperplasia

CONCLUSIONS: The prevalence of endometrial carcinoma in patients who had a community hospital biopsy diagnosis of AEH was high (42.6%). When considering management strategies for women who have a biopsy diagnosis of AEH, clinicians and patients should take into account the considerable rate of concurrent carcinoma. Cancer 2006. © 2006 American Cancer Society.
Behavior of hyperplasia

Follow-up of hyperplasia and atypical hyperplasia in 176 patients

<table>
<thead>
<tr>
<th>Type of hyperplasia</th>
<th>No. of patients</th>
<th>Regressed</th>
<th>Persistent</th>
<th>Progressed to carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplasia</td>
<td>122</td>
<td>97 (80%)</td>
<td>23 (19%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>40</td>
<td>29 (73%)</td>
<td>8 (20%)</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

Follow-up of simple and complex hyperplasia and atypical hyperplasia in 176 patients

<table>
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<tbody>
<tr>
<td>Simple</td>
<td>104</td>
<td>84 (81%)</td>
<td>14 (13%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Complex</td>
<td>22</td>
<td>12 (55%)</td>
<td>7 (32%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Simple atypical</td>
<td>13</td>
<td>9 (69%)</td>
<td>3 (23%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Complex atypical</td>
<td>15</td>
<td>12 (80%)</td>
<td>2 (13%)</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

Age is Important

<table>
<thead>
<tr>
<th>Age</th>
<th>Preoperative (40 years or &lt; 40 years)</th>
<th>Metaplastic (50 years or &gt; 50 years)</th>
<th>Postmenopausal (50 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>(%)</td>
<td>No.</td>
<td>(%)</td>
</tr>
<tr>
<td>64</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>29</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

EDEMETRIOID ADENOCARCINOMA

Architectural grading of endometrial carcinoma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No more than 5% of the tumor is composed of solid masses</td>
</tr>
<tr>
<td>2</td>
<td>6–50% of the tumor is composed of solid masses</td>
</tr>
<tr>
<td>3</td>
<td>More than 50% of the tumor is composed of solid masses</td>
</tr>
</tbody>
</table>
Morphologic Variants of Type I

Endometrioid Carcinoma Grade 2

Endometrioid Carcinoma Grade 3
Endometrioid Carcinoma Grade 3

Endometrial Tumorigenesis

Endometrial Intraepithelial Carcinoma

EIC is characterized by markedly atypical nuclei, identical to those of invasive serous carcinomas, lining the surfaces, and glands of the atrophic endometrium.

The lesion can be very small and focal and is often present on the surface of a polyp.

EIC often has a slightly papillary contour and some cells display hobnail morphology and smudged, hyperchromatic nuclei.

The nuclei are enlarged, and frequently display enlarged eosinophilic nucleoli.

Numerous mitotic figures, including atypical ones, are present. On occasion, the abnormal proliferation involves only a portion of an endometrial gland.
Endometrial Intraepithelial Carcinoma

Minimal Serous Carcinoma

UTERINE SEROUS CARCINOMA

- Histopathological
  - Often papillary architecture (may be glandular)
  - Markedly atypical cells
  - Arises in the setting of atrophy
  - Resembles ovarian serous carcinoma
  - All high grade (FIGO Grade 3)

- Clinical
  - Older women
  - Not associated with estrogen
  - Aggressive behavior
  - Requires thorough staging (even EIC)
  - Women with "true" stage 1 USCs have a favorable prognosis
Genetic Alterations Distinguish Endometrioid from Serous Endometrial Carcinomas

Endometrioid Carcinoma
- TP53 mutations relatively uncommon (except high grade)
- microsatellite instability present in approximately 20%
- PTEN mutations common (>50%)
- K-RAS and CTNNB1 mutations common

Serous Carcinoma
- TP53 mutations extremely common (nearly 100%)
- PTEN, K-RAS, CTNNB1 mutations uncommon
- microsatellite instability uncommon
Endometrial Tumorigenesis

- Estrogen
- PTEN
- SH
- CH
- CAH
- Endometrioid Ca
- MI
- K/RAS
- PIK3CA
- p53
- Nl epithelium
- Atrophy
- EIC
- Serous Ca
- p53

Other Type 2 Endometrial Carcinomas

- Clear cell carcinoma
- Malignant mullerian mixed tumors (MMMT)
- Undifferentiated carcinoma

Clear Cell Carcinoma
INHERITED FORMS OF ENDOMETRIAL CARCINOMA

Lynch Syndrome
- Germline mutations in DNA mismatch repair genes
- Most common are MLH1 and MSH2
- Results in MSI
- Approximately 1/50 women with EC will have LS
- 25-30% of sporadic EC have MSI
- Currently routine screening with IHC is not being done

Cowden Disease
- Germline mutations in PTEN
- 1/200,000 individuals
- 5-10% lifetime risk compared to 2.6%
- Blind endometrial biopsies starting at 35-40 or 5 years prior to earliest diagnosis of EC in the family
Gross Examination of a Hysterectomy for Endometrial Cancer

1. Orient the uterus. The round ligaments are most anterior, and the ovaries, if present, are most posterior. The peritoneum extends further inferiorly along the posterior aspect of the uterus than it does anteriorly.

2. Weigh and measure the specimen. Ink the paracervical and parametrial soft tissue margins (we also ink the serosa of uterus even though it is not a margin).

3. Place a probe through the endocervical canal into the endometrium. Bivalve the uterus into anterior and posterior halves with a long blade.

4. Longitudinally section the cervix, extending the incision upward through the LUS. Serially bread-loaf the uterine corpus with 0.5 cm transverse slices.

5. Describe the size, appearance, and location of the tumor, and the depth of myometrial invasion.

6. Submit sections of the tumor at the deepest point of invasion, anterior and posterior LUS and cervix, uninvolved endometrium. Submit sections of ovaries and the entire fimbriated end of the fallopian tube. If no lesion is visible submit the entire endometrium.
**Endometrial Carcinoma Staging**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>IA</td>
<td>Tumor limited to the endometrium, no evidence of myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor invasion of the myometrium, ≤ 50% of the myometrial thickness</td>
</tr>
<tr>
<td>IC</td>
<td>Tumor invasion of the myometrium, &gt; 50% of the myometrial thickness</td>
</tr>
<tr>
<td>IA1</td>
<td>Tumor limited to the endometrium, no evidence of myometrial invasion, no lymphovascular invasion</td>
</tr>
<tr>
<td>IB1</td>
<td>Tumor invasion of the myometrium, ≤ 50% of the myometrial thickness, no lymphovascular invasion</td>
</tr>
<tr>
<td>IC1</td>
<td>Tumor invasion of the myometrium, &gt; 50% of the myometrial thickness, no lymphovascular invasion</td>
</tr>
<tr>
<td>IA2</td>
<td>Tumor limited to the endometrium, lymphovascular invasion</td>
</tr>
<tr>
<td>IB2</td>
<td>Tumor invasion of the myometrium, ≤ 50% of the myometrial thickness, lymphovascular invasion</td>
</tr>
<tr>
<td>IC2</td>
<td>Tumor invasion of the myometrium, &gt; 50% of the myometrial thickness, lymphovascular invasion</td>
</tr>
<tr>
<td>IB3</td>
<td>Tumor invasion of the myometrium, &gt; 50% of the myometrial thickness, lymphovascular invasion, positive peritoneal washings</td>
</tr>
</tbody>
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**Summary**

**Goals - The learner will understand:**
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- The major types of endometrial cancer
- The clinical relevance in the distinction of different types of endometrial cancer

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